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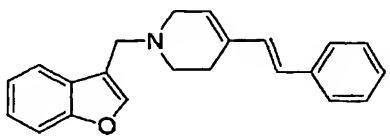
Published:
— *with international search report*

... other abbreviations, refer to the "Guid... Abbreviations" appearing at the begin... of the PCT Gazette.

WO 03/080055 A1

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING A BENZOFURAN DERIVATIVE AND THEIR USE FOR THE TREATMENT OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER



(I)

(57) Abstract: The compound of formula (I): or a pharmaceutically acceptable salt thereof, especially the mesylate salt, is of use in a method for the treatment and/or prevention of attention-deficit/hyperactivity disorder (ADHD).

PHARMACEUTICAL COMPOSITIONS COMPRISING A BENZOFURAN DERIVATIVE AND THEIR USE FOR THE TREATMENT OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER

This invention relates to the use of a particular heteroaromatic compound. More particularly, the invention is concerned with the use of a (1,2,3,6-tetrahydropyridin-1-yl)methyl substituted benzofuran derivative which is a selective antagonist of the dopamine D_4 receptor subtype within the brain and is therefore of benefit in the treatment and/or prevention of attention-deficit/hyperactivity disorder (ADHD).

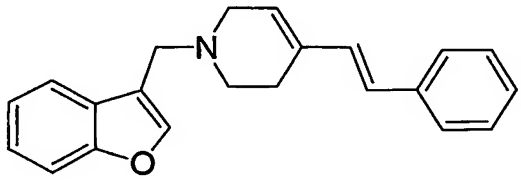
ADHD is a condition characterised by inattentive, impulsive hyperactive behaviour, and affects some 6% of school age boys in the USA. Although primarily affecting children, in some cases the symptoms persist into adulthood. Several recent studies have implicated the dopamine D_4 receptor in the etiology of ADHD (see, for example, Zhang *et al.*, *Neuropsychopharmacology*, 2001, **25**, 624-632, and references therein).

EP-A-[illegible]792 relates to the use of a dopamine D_4 receptor ligand in the treatment or prevention of a novelty-seeking disorder, including attention deficit disorder with hyperactivity disorder. There is in that publication, however, no disclosure nor any suggestion of employing the specific benzofuran derivative of formula I as depicted below, or a pharmaceutically acceptable salt thereof, in the therapy of ADHD.

WO 02/072029, published on 19 September 2002, describes and claims a method of inhibiting motor hyperactivity in a mammal exhibiting the symptoms of ADHD, which comprises administering thereto a compound selected from a list of known dopamine D_4 receptor antagonists. That list does not, however, include the compound of formula I as depicted below or a pharmaceutically acceptable salt thereof.

US Patent No. 5,665,722 discloses a class of substituted benzofuran derivatives which are selective dopamine D_4 receptor antagonists and which are said to be useful in the treatment of schizophrenia.

According to the present invention, there is provided a method of treating or preventing ADHD comprising administering to a subject in need thereof a therapeutically-effective amount of the compound of formula I:



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or a pharmaceutically acceptable salt thereof.

Many of the known dopamine D_4 receptor antagonists, e.g. L-745,870 (cf. WO 02/072029), incorporate an indole or aza-indole ring system into their molecular structure, and are accordingly susceptible to being metabolised by a retro-Mannich mechanism, leading to the formation of potentially toxic by-products, e.g. covalent glutathione adducts. The molecular structure of the benzofuran derivative of formula I above, meanwhile, is devoid of an indole or aza-indole ring system; use of this compound in the therapy of ADHD is therefore advantageous, in that there is consequently no possibility of metabolism by a retro-Mannich route.

In one embodiment of the present invention, the subject is a human male. In this embodiment, the subject is typically a human male aged 5-18 years, preferably aged 12-18 years.

The method of treatment according to the invention typically comprises administering to the subject a tablet containing from 1 to 100 mg of the compound of formula I or pharmaceutically acceptable salt thereof once, twice, three times or four times a day. Preferably, the tablet contains from 2 to 50 mg, more preferably from 5 to 25 mg, of the compound of formula I or pharmaceutically acceptable salt thereof, and is administered once or twice a day. In a particular embodiment, a tablet

containing 15 mg of the compound of formula I or pharmaceutically acceptable salt thereof is administered once a day.

The method of treatment according to the invention may be used for treatment of ADHD which is of the combined type, or which is of the predominantly inattentive type, or which is of the predominantly hyperactive-impulsive type.

There is further disclosed the use of the compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treatment or prevention of ADHD.

For use in medicine, the salts of the compound of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compound of use in the invention or of its pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compound of use in this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound of use in the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, methanesulphonic acid, carbonic acid or phosphoric acid. Examples of preferred salts include the methanesulphonate (mesylate) salt.

The medicaments relevant to the invention are typically pharmaceutical compositions comprising the compound of formula I, or pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active

compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of the compound of formula I, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of use in the present invention. Favoured unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 15, 25, 50 or 100 mg, of the active ingredient. The tablets or pills can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the compositions relevant to the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed

oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of ADHD, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

In order to alleviate the symptoms of ADHD without causing sedation or extrapyramidal side-effects, the dosage level of the compound of formula I may be selected such that the dose administered is effective in substantially completely blocking the dopamine D_4 receptor subtype in human brain whilst displaying no or negligible dopamine D_2 receptor subtype occupancy. A suitable dosage level in this regard is about 0.001 to 5.0 mg/kg per day, more particularly about 0.005 to 1.0 mg/kg per day, and especially about 0.01 to 0.5 mg/kg per day.

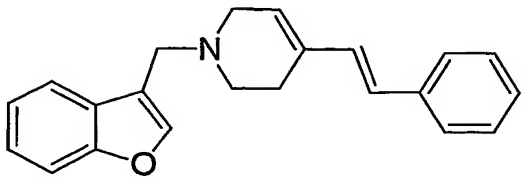
EXAMPLE 1

Use of the compound of formula I for treatment of ADHD

The mesylate salt of the compound of formula I is prepared as described in Example 1 of GB 2,306,471. Tablets comprising 15 mg of this active ingredient are prepared by conventional means and a single tablet is administered once a day to a subject suffering from, or prone to, ADHD.

CLAIMS:

1. The use of the compound of formula I:



I

or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treatment or prevention of ADHD.

2. The use as claimed in claim 1 wherein the medicament contains the mesylate salt of the compound of formula I as defined in claim 1.

3. A method of treating or preventing ADHD comprising administering to a subject in need thereof a therapeutically-effective amount of the compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof.

4. The method as claimed in claim 3 wherein the compound administered is the mesylate salt of the compound of formula I as defined in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/01237

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/44 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 2 306 471 A (MERCK SHARP & DOHME) 7 May 1997 (1997-05-07) cited in the application page 1, line 8,9 page 2, line 13-15 example 1 ---	1-4
Y	TARAZI F I ET AL: "Dopamine D4 receptors: significance for molecular psychiatry at the millennium." MOLECULAR PSYCHIATRY. ENGLAND NOV 1999, vol. 4, no. 6, November 1999 (1999-11), pages 529-538, XP009012526 ISSN: 1359-4184 the whole document --- -/--	1-4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 2003	07/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veronese, A

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	LICINIO J: "The dopamine D4 receptor and attention deficit hyperactivity disorder." MOLECULAR PSYCHIATRY. ENGLAND MAY 1996, vol. 1, no. 2, May 1996 (1996-05), pages 83-84, XP009012525 ISSN: 1359-4184 the whole document	1-4
A	EP 1 177 792 A (PFIZER PROD INC) 6 February 2002 (2002-02-06) cited in the application claims 1,12	1-4
P,Y	WO 02 072029 A (MCLEAN HOSPITAL CORP) 19 September 2002 (2002-09-19) page 3, line 21 -page 4, line 16; claims	1-4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/01237

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 3,4 are directed to a method of treatment of the human / animal body, the search has been carried out and based on the alleged effects of the compound / composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

[redacted]nformation on patent family members

[redacted]onal Application No
PCT/GB 03/01237

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2306471 A	07-05-1997	US 5681836 A	28-10-1997
EP 1177792 A	06-02-2002	EP 1177792 A2	06-02-2002
		JP 2002104969 A	10-04-2002
		US 2002049209 A1	25-04-2002
WO 02072029 A	19-09-2002	WO 02072029 A2	19-09-2002
		US 2002187920 A1	12-12-2002